REVIEW

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ONCOLOGICAL EMERGENCIES

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Summary

Emergency conditions in oncology may arise either as part of the malignant disease itself, or may be associated with its treatment. They are potentially life-threatening conditions that require urgent care, often with patient hospitalization and a multidisciplinary treatment approach. Consequently, it is important that all physicians are familiar not only with potential oncological emergencies which may occur in their clinical practice but also how to provide the most effective care in a timely fashion. In this review article we comprise the clinical features and treatment of several of these emergencies, namely the superior vena cava syndrome (SVCS), elevated intracranial pressure, metastatic spinal cord compression (MSCC), hypercalcemia and febrile neutropenia.

KEY WORDS: *oncological emergency, febrile neutropenia, hypercalcemia, raised intracranial pressure, superior vena cava syndrome, spinal cord compression*

HITNA STANJA U ONKOLOGIJI

Sažetak

Hitna stanja u onkologiji mogu nastati kao posljedica prisustva maligne bolesti ili mogu biti povezana s liječenjem. To su stanja potencijalno opasna po život koja zahtijevaju hitno zbrinjavanje, često uz hospitalizaciju bolesnika, te multidisciplinarni terapijski pristup. Stoga je važno da svi liječnici budu upoznati s mogućim hitnim onkološkim stanjima koja se mogu pojaviti u njihovoj kliničkoj praksi i kako na vrijeme pružiti najučinkovitije liječenje. U ovom preglednom članku obuhvatili smo klinička obilježja i liječenje sindroma gornje šuplje vene, povišenog intrakranijskog tlaka, metastatske kompresije leđne moždine, hiperkalcemije i febrilne neutropenije.

KLJUČNE RIJEČI: *hitno stanje u onkologiji, febrilna neutropenija, hiperkalcijemija, povišen intrakranijski tlak, sindrom gornje šuplje vene, kompresija leđne moždine*

INTRODUCTION

An oncological emergency is an acute event related to a patient's tumor or its treatment, which, if left untreated, can lead to morbidity or death. Worldwide, cancer is the second cause of death after cardiovascular diseases (1). The advances in oncology and the subsequent growing population of cancer survivors necessitate familiarity with the diagnosis and treatment of common oncological emergencies. Unique complications that require an urgent evaluation are often left to general and emergency department practitioners. Timely diagnosis and treatment can significantly improve the quality of life and decrease the mortality rate of patients with malignant disease who present to the emergency department (2). Sometimes, an emergency can be the initial presentation of cancer, particularly metastatic spinal cord compression (MSCC) or superior vena cava syndrome (SVCS). A recent retrospective cross-sectional study showed that the most common type of neoplasm in cancer patients who visited the emergency department was a solid metastatic lesion, located in either the brain or the gastrointestinal tract, in stage III and IV, and found in patients currently undergoing chemo- and/or radiotherapy (2).

The most common emergencies, which are discussed in this paper, include SVCS, MSCC, raised intracranial pressure, hypercalcemia, and febrile neutropenia.

SUPERIOR VENA CAVA SYNDROME (SVCS)

Superior vena cava syndrome (SVCS) is caused by the compression of the superior caval vein, its tumor invasion or a intraluminal thrombus inside of it. Subsequently, the venous drainage from the head, neck, thorax, and upper extremities is impaired, and the cardiac output is decreased. The most common malignancies associated with this condition are lung cancer (75%), lymphoma (15%), and metastatic disease (3).

No correlation has been found between symptom duration and long term outcome for most cases of SVCS, regardless of the treatment performed (radiation, stenting, or chemotherapy) (4). The disease usually advances slowly, resulting in the development of collateral circulation in the azygous venous system. However, sometimes a rapid obstruction of the vein occurs, causing raised intracranial pressure and cerebral edema. Patients typically present to the ER with shortness of breath accompanied with facial and upper extremity edema with venous dilatation of the neck as well as the thoracic wall (5). Considering the slowly advancing nature of the disease, SVCS is rarely an acute emergency, enabling enough time to perform diagnostic workup. If there is no histological/cytological evidence of malignancy, a chest X-ray, a CT scan of the thorax, and a biopsy should be performed (5).

The treatment and prognosis of this condition depend on the underlying disease. Initial treatment includes a sitting position for the patient, oxygen therapy if necessary, and corticosteroids with gastric protection. A vena cava stent can be implanted in order to alleviate symptoms and allow sufficient time to acquire a histological confirmation. If present, thrombosis should be treated (3).

Radiotherapy has been considered for a long time as the quickest treatment for symptom relief, with or without the addition of steroids. Symptoms usually improve in 3-9 days. However, worth noting is that, in some cases, improvement hasn't been reported until up to 30 days after the initial treatment (6). Also, percutaneous stenting has been proven to relieve symptoms within hours of the procedure, but it should only be considered for patients for which other treatment options are limited (e.g., patients with mesotheliomas) (7).

While urgent chemotherapy is an option for chemosensitive tumors such as lymphomas, radiotherapy remains the treatment of choice for solitary tumors causing this condition (3). During radiation therapy procedure, the patient should lie on his back, and the radiation field should not only include the tumor and mediastinum, but the superior vena cava as well. The doses depend on the patients' performance status (PS). For patients with a poor PS, a single dose of 10 Gy or 16 Gy in two doses delivers reasonable symptom control if the field size is smaller than 12x12cm. Patients with good PS and a localized disease can receive 36 Gy in 12 fractions. Carefully selected patients with lung cancer can receive a radical dose (3).

ELEVATED INTRACRANIAL PRESSURE

Brain metastases are the most common cause of increased intracranial pressure in cancer pa-

tients, with melanoma and lung cancer being the most frequent primary lesion. Other causes of elevated intracranial pressure include brain hemorrhage, cerebral edema, or infection (8). Most patients develop symptoms over days or weeks, with morning headache being the most common presenting symptom. Focal neurologic deficits and epileptic seizures, can also frequently be a presenting symptom(8). After the physical exam and blood test, a brain CT scan should be the next step in the diagnostic workup. A lumbar puncture can be used to measure cerebral spinal fluid pressure. However, it MUST not be performed before a CT scan excludes any neoplastic lesions, in which case a lumbar puncture is contraindicated. A brain MRI can be useful in the differentiation between neoplastic, infectious, and ischemic processes (3).

In some cases, such as in patients with hydrocephalus, an urgent neurosurgical intervention is sometimes necessary. In patients with vasogenic edema, mannitol 20-25% with dexamethasone or even mechanical hyperventilation can be useful. Fluid overload should be avoided (8). Radiotherapy is used for the treatment of patients with brain metastases. If the patient has more than three brain metastases, a whole-brain radiation remains the standard of care. However, if the patient presents with three or less metastases, stereotactic ablative radiotherapy or surgery can be considered (3).

SPINAL CORD COMPRESSION

Metastatic spinal cord compression (MSCC) is defined as spinal cord or cauda equina compression, either by direct pressure and/or induction of vertebral collapse, instability by metastatic spread or by direct extension of the malignant lesion (3). An Ontario population-based study found that the cumulative probability of experiencing at least one episode of MSCC in the five years preceding death from cancer was 2.5% overall, and ranged from 0.2% in cancer of the pancreas to 7.9% in myeloma (9). Spinal cord compression is the second most frequent neurological complication of cancer, the first one being brain metastases (8). This condition is commonly associated with breast, lung, and prostate cancer, as well as multiple myeloma (3). Signs and symptoms depend on the level of compression. Seeing as the spinal cord ends at the level of the first lumbar vertebrae, compression below this level results in lower motor neuron symptoms, and compression above L1, upper motor neuron symptoms. Muscle weakness usually develops before sensory or autonomous nervous system symptoms (3). Current NICE guidelines recommend informing patients not only about the risk of developing MSCC and its possible symptoms, but also advises on what to do if they develop them (10).

MRI should be performed when there is a suspected MSCC, or a CT scan if there is a contraindication for MRI. NICE guidelines recommend an MRI within one week of symptom development. Plain radiographs are not recommended for the diagnosis of MSCC (10).

A multidisciplinary approach is necessary when dealing with this condition. Surgery should be performed to prevent cases of MSCC and in selected patients with vertebral metastases accompanied by spinal instability or unmanageable pain. Surgery should also be considered in patients who have already developed MSCC but have a good prognosis and the remaining ability to walk, sensory or motor functions. Patients should start treatment with dexamethasone 16mg daily while awaiting radiotherapy or surgery, after which the dose should be gradually reduced during 5-7 days, and then stopped. Fractionated radiotherapy should be offered as the definitive treatment of choice to patients with epidural tumors without neurological impairment, mechanical pain, or spinal instability and to patients with a good prognosis who are having radiotherapy as their first-line treatment. Postoperative fractionated radiotherapy should be offered to all patients with a good surgical outcome. Patients with tetra- or paraplegia lasting for more than 24 hours or have an overall poor prognosis should not be offered urgent radiotherapy (10).

A recently published meta-analysis showed better local control rates, but with no difference in survival rates and motor function outcome in patients who received long course radiotherapy (>2 weeks) compared to short course radiotherapy (<2 weeks). Considering better patient's compliance as well as a possible lower cost of treatment, short course radiotherapy remains a viable treatment option (11).

HYPERCALCEMIA

Hypercalcemia is defined as a serum calcium level over 2.6 mmol/L. In patients who have bone

metastases, skeletal resorption is the leading cause of elevated serum calcium. In other patients, hypercalcemia can be also caused by circulating factors such as parathyroid hormone-related peptide- PTH-RP and 1,25 dihydroxy vitamin D. Malignant hypercalcemias have a poor prognosis (3). Over 30% of patients with advanced solid tumors develop malignant hypercalcemia, with symptoms such as nausea, vomiting, obstipation, stomachache, tiredness, polyuria, polydipsia, and confusion. If left untreated, hypercalcemia leads to coma and death (8).

Lab blood tests are the fastest and first step in diagnosing hypercalcemia. An ECG can show a prolonged PR interval and wide QRS complexes (8). The treatment of this condition depends on the level of calcium. Patients with serum levels under 3.0 mmol/L should be adequately hydrated, advised to keep active, and be closely monitored. In the case of higher calcium levels, 3 liters of the saline solution should be administered for 24 hours, with careful monitoring or urine excretion, which should be 100-150 mL/h. Thiazide diuretics are not advised, furosemide application should be held off until dehydration correction (3). Bisphosphonates promote the apoptosis of osteoclasts actively engaged in the degradation of mineral on the bone surface and have a quick and long term effect. Zoledronate is currently the best choice for these patients, achieving serum calcium normalization in 4 to 6 weeks, but caution is advised for possible side effects such as jaw osteonecrosis (8).

FEBRILE NEUTROPENIA

Neutropenia associated with fever can be a severe and life-threatening complication of chemotherapy. NICE defines febrile neutropenia as a fever over 38°C or other clinical signs of infection in patients receiving chemotherapy whose absolute neutrophil count (ANC) is 0.5×10 9/L or lower (8).

Pathogens that cause febrile neutropenia include gram-negative bacteria (*P. aeruginosa, E. coli, Kl. pneumoniae*) and gram-positive bacteria (*staphylococcus spp., streptococcus spp., enterococcus spp.).* No specific organism can be identified in 75-80% of cases (8). Patients usually present with fever, low ANC, and a history of recent chemotherapy applications. Hypotension is a dangerous complication that can lead to multiple organ failure (kidney, brain, liver) (3). All patients with a suspected diagnosis of febrile neutropenia should have a full blood count, kidney and liver function tests, CRP, blood cultures, and urine tests. Additional investigations, such as chest and abdomen X-ray, should be done based upon clinical presentation (3).

Patients can be stratified based on the risk of serious complications using the MASCC Risk-Index score (Multinational Association for Supportive Care in Cancer – MASCC). MASCC takes into account the presence or absence of hypotension, burden of illness, history of chronic obstructive pulmonary disease, history of fungal infection, volume status, tumor type (solid vs. liquid), and age. A patient with a total score of 21 or higher is considered as a lower risk one and can be treated as an outpatient. Broad-spectrum antibiotics should be administered within 60 minutes once NF is identified, and appropriate cultures have been obtained (12). Recommendations for outpatient patients are ciprofloxacin 750 mg twice daily with amoxicillin/clavulanate 500 to 125mg every 8 hours or moxifloxacin alternatively. Outpatient therapy should be continued for seven days or at least until the patient has been afebrile for 4-5 days, with daily visits. High-risk patients (MASCC score higher than 21) should be hospitalized for IV antibiotic application and monitoring. Once the diagnosis has been made and the cultures were drawn, empiric IV antibiotics should be started. Monotherapy (cefepime, meropenem, zosyn) and dual therapy (an aminoglycoside in addition to either piperacillin, cefepime, ceftazidime) agents are commonly used. However, if there is an increased risk of gram-positive bacteremia (patients with catheter-related infections, severe sepsis with hypotension) an additional antibiotic should be added, usually vancomycin. It is important to recognize signs of septic shock as these patients should be transported into an intensive care unit. If, after four days, myeloid recovery does not appear to be imminent, a CT scan of sinuses and lungs can be considered, with adding antifungal therapy (8, 12).

CONCLUSION

Oncological emergencies may be seen in any emergency medical service and will become more

frequent as our population ages and more patients are treated because of malignant diseases. Physicians can, therefore, expect to meet such patients in emergency departments as well as in outpatient clinics. Quick evaluation and diagnosis with the introduction of proper therapy can save lives and prevent irreversible morbidity. The management of oncological emergencies requires a multidisciplinary approach, and it is essential that all health care professionals have sound knowledge of these conditions.

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